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IGF2BP3 inhibition: another home run for RNA-binding protein targeting in hematological malignancies

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RNA-binding proteins (RBPs) are critical regulators of gene expression, affecting RNA processing till translation. More than 1,500 proteins have been catalogued as RBPs in the human genome. [1] RBPs are very diverse in respect to structure, characteristic of RNA binding domain and function. In fact, RBPs are notoriously multi-functional with some of them showing great target diversity and ability to bind both mRNA and different types of ncRNAs. By orchestrating the expression of gene networks, RBPs modulate complex biological processes such as differentiation and cell fate decisions. [2] In cancer, aberrant expression of RBPs has been reported over the years in multiple tumor solid tumors and hematological malignancies. Their subsequent molecular characterization and genomic analysis led to the identification of "oncogenic" RBPs and provided maps of their target genes. Despite their relevance and established role in tumorigenesis, RBPs have not been fully explored as candidate targets in cancer therapy. Targeting these proteins offers a powerful strategy to simultaneously modulate multiple oncogenic pathways due to their broad regulatory impact on numerous transcripts. [3,4] Barriers to select candidates such as characteristics of RNA binding motifs, essential regulatory role in normal cells and pattern of expression have discouraged systematic investigation of RBPs as therapeutic targets. The brave work of several research groups kept the field alive. Many identified RBP inhibitors showed excellent potential in pre-clinical and clinical studies. Some protein families that include Musashi, hnRNPs and ELAV received special attention. In hematological malignancies, two success stories should be highlighted. Splicing Factor 3B Subunit 1 (SF3B1) is the most recurrently mutated gene in myelodysplastic syndrome (MDS) and Chronic Lymphocytic Leukemia (CLL). Mutant SF3B1 creates a cancer dependency, accelerates the onset and increases leukemogenesis. Several SF3B1

inhibitors have been developed and are currently being evaluated in clinical trials. [5] Nucleophosmin 1 (NPM1) is a multi-function RBP, being particularly relevant in ribosome biogenesis. NPM1 mutations occur in more than 30% of de novo AML and promote re-localization of the protein to the nucleus. Mutant NPM1 interacts with the menin-KMT2A complex, activating stem-cell programs. An inhibitor of this interaction induced complete remissions in acute myeloid leukemia (AML) with an NPM1 mutation, and the drug was recently approved by the FDA for therapeutic use. [6]

The Insulin-like growth factor 2 mRNA-binding protein (IGF2BP) family, which includes IGF2BP1, IGF2BP2, and IGF2BP3, checks all the boxes as ideal therapeutic target. These oncofetal proteins are highly expressed during embryogenesis but barely detectable in most adult tissues. IGF2BP expression gets re-activated in tumors and high levels of expression of these RBPs have been detected in diverse cancers. They stabilize and enhance the translation of potent oncogenes like *MYC*, *CDK6*, and *HOX9*. Their regulatory roles, mechanism of action and binding motifs are well characterized, providing additional information to develop strategies for the identification of inhibitors. [7]

IGF2BP3 is up-regulated in MLL-translocated B-ALL. Previous work from the Rao lab established that its deletion delays leukemia development and extends leukemia free survival.[8,9] In this issue, Jaiswal et al. [10] reported their findings on a novel IGF2BP3 inhibitor that showed excellent results in pre-clinical studies. The authors used a strategic screening platform that took advantage of IGF2BP3's unique RNA binding motif, which includes an m6A modification. A common tactic used in RBP inhibition is to disrupt the RBP-RNA interaction by using competing molecules. They screened close to 200,000 compounds in a TR-FRET assay that used a GFP-tagged IGF2BP3 protein and a biotinylated RNA oligo with a target sequence. The top hit compound, I3IN-002, showed excellent results *in vitro* in particular against B-ALL cells lines with MLL-AF4 translocation. *In vivo*, treatment expanded leukemia-free survival. I3IN-002 was not the first identified IGF2BP3 inhibitor but it was the first to be tested against hematological malignancies and the first proven to efficiently disrupt IGF2BP3's binding to its target RNAs and affect their expression. A key finding was the significant enrichment of compounds with an indolyltriazine group among the top hits in the screening. These results suggest that indolyltriazine groups might favor RNA-protein binding, a hypothesis meriting further structural investigation. These results could provide important information and fast-track the development of inhibitors against other oncogenic RBPs.

While I3IN-002 is not yet ready to move to the clinic, the results are very promising. With focused medicinal chemistry optimization, we will soon see an IGF2BP3 inhibitor ready for therapeutic use. Overall, the results of Jaiswal and colleagues serve as motivation for the scientific community to keep exploring RBP targeting as alternative therapeutic routes.

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Figure 1. I3IN-002 disrupts the interaction between the oncogenic RNA binding protein IGF2BP3 and its RNA targets.